

REMARKS

Status of the Claims

Claims 1, 6-9, 15 and 21 are pending, with claims 1 and 21 being independent. Claims 6 is amended herein. Support for the claim amendments can be found throughout the specification and claims as filed. As such, no new matter has been added.

Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks.

Applicants respectfully request an interview with the Examiner to discuss outstanding issues. The Examiner is invited to contact Applicants' representative in this regard to discuss a potential interview.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 6 stands rejected under 35 U.S.C. § 112, second paragraph, for the recitation of "is comprised between". Claim 6 is amended herein to replace this phrase with "is between". Applicants request that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

Claim 1, 6-9, 15, and 21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Brulls (U.S. Patent No. 6,730,685) in view of Mangel (WO 01/56573). Applicants respectfully traverse.

Brulls discloses formulations that comprise a water free or almost water free polyethylene glycol solution of sodium or potassium salt of a PPI derived from benzimidazole. These formulations are useful for inhibiting gastric acid secretion in mammals. The formulations in the examples of Brulls contain omeprazole. Tenatoprazole is only mentioned in the list of PPIs at the top of column 5. However, nothing in Brulls indicates that tenatoprazole is preferred or exhibits particular properties over other PPIs.

Further, Brulls fails to disclose any combination of one PPI with a NSAID. The skilled artisan would prefer the use of omeprazole, alone or in combination with other drugs such as NSAIDs, antibacterial compounds, motility stimulating drugs, anti-acids and/or H₂-blockers.

Mangel does not remedy Brulls. Mangel discloses anti-inflammatory agents of the COX₂-inhibitors series which are likely to increase the gastro-intestinal motility. Among the very numerous compounds listed in this document, celecoxib and rofecoxib are mentioned,

for example at page 5, lines 7-8. Mangel also indicates that COX-2 inhibitors can be administered in combination with one or more other therapeutic agent(s) and mentions as examples different categories of drugs such as PPIs (page 8, lines 15-17). In this list omeprazole is mentioned in the first position while tenatoprazole is cited at the final end of the list. However, the examples do not disclose any combination of a COX2-inhibitor with a PPI. Accordingly, Mangel and Brulls, taken in combination, do not disclose to a pharmaceutical composition comprising an anti-inflammatory agent selected from a nonsteroidal anti-inflammatory agent (NSAID) or a cyclooxygenase-2 inhibitor, in combination with tenatoprazole.

The present invention provides a pharmaceutical composition with anti-inflammatory properties which treats the symptoms of pain and inflammatory diseases, while avoiding the adverse side effects associated with the use of anti-inflammatory agents. As previously discussed, studies performed with the present invention show that the combination of tenatoprazole and an anti-inflammatory agent selected from those recited in claim 1 achieves unexpected benefits and uses when compared with other PPIs and with anti-inflammatories used alone or in combination. The specific combination as claimed herein allows for the control of gastric acidity, along with an anti-inflammatory activity which provides improved efficacy and better safety than known therapies. These advantages result from a specific tenatoprazole activity which complements that of the claimed anti-inflammatory agents, and which is not exhibited by other proton pump inhibitors.

As shown on pages 6-8 of the present specification, tenatoprazole differs from other PPIs in its much longer elimination half-life, and also in its considerable degree of tissue exposure. The pharmacokinetics studies performed show that tenatoprazole exhibits a long half-life and high AUC values (area under the curve), providing evidence of a low rate of metabolism and/or high bioavailability. Accordingly, the prolonged exposure linked to the long elimination half-life of tenatoprazole, and demonstrated by the AUC value, allows tenatoprazole to remain at the site of activity in the body for a much longer time than other PPIs, and thus provides a pharmacodynamic effect which is prolonged over time.

Experiments have shown that tenatoprazole is endowed with a plasma half-life/ pump regeneration time ratio which is notably higher than that seen with other PPIs, thus permitting its use in pathologies where currently available medicinal products have little

effect. It can be particularly useful in treating the nocturnal symptoms of gastroesophageal reflux and gastro-duodenal ulcers.

Therefore, when it is combined with one of the anti-inflammatory agents recited in the present claims, tenatoprazole, as compared with other PPIs, provides significant advantages with respect to suppressing gastric acidity. This combination allows effective action on the nocturnal peak of gastric acidity and on nocturnal symptoms in patients suffering from gastroesophageal reflux, in which it achieves marked relief, even in patients refractory to classic therapies with standard PPIs such as omeprazole. These particular properties of tenatoprazole were unexpected and not known from the prior art at the time the invention was made, and these benefits are certainly not disclosed in the cited references. Therefore, even if the one skilled in the art had combined the teaching of Brulls and Mangel, they would not arrive at the claimed invention.

Claims 1, 6-7, 9, 15, and 21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chih-Ming (WO 02/22108) in view of Mangel and Naesdal (*European Journal of Gastroenterology and Hepatology*, 2001, 13:1401-1406).

Chih-Ming discloses a solid composition comprising a NSAID extended release tablet and an enterically coated proton-pump inhibitor without a separating layer between the PPI and the enteric coat. As discussed in the present specification, this type of combination as disclosed in Chih-Ming does not provide a specific combination of active ingredients but instead provides a new dosage form. Among NSAIDs, only diclofenac is mentioned by Chih-Ming and among PPIs, only omeprazole is mentioned. Tenatoprazole is not disclosed at all. Naesdal also fails to disclose tenatoprazole, as the only disclosed PPI is omeprazole.

Therefore, even if the one skilled in the art had combined the teaching of Chih-Ming, Mangel and Naesdal, they would not arrive at the claimed invention. Instead, the skilled artisan would pursue a therapy containing omeprazole.

Claims 1, 6-9, 15, and 21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chih-Ming in view of Mangel and in further view of Bergstrand (U.S. Patent No. 5,753,265).

Bergstrand does not cure the deficiencies of Chih-Ming, Mangel, and Naesdal, as discussed above. Bergstrand discloses pharmaceutical compositions containing a PPI and

lists different compounds, including tenatoprazole. There is no mention at all of the newly discovered unexpected pharmacokinetic properties of tenatoprazole. Tenatoprazole is not mentioned as a preferred compound and is not used in the formulation examples. Accordingly, there is no motivation to combine tenatoprazole with one of the anti-inflammatory agents recited in amended claim 1.

At least in light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

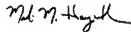
CONCLUSION

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary for a timely response, this paper should be considered as a petition for an Extension of Time, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #104006.B130121).

Respectfully submitted,

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